Searching for the Frequency of Cardiac Transthyretin Amyloidosis among Elderly Heart Failure Patients Noninvasively Using ^{99m}Tc-labeled Pyrophosphate Scintigraphy

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Background : The diagnosis of cardiac transthyretin (ATTR) amyloidosis is frequently delayed or missed because of its nonspecific echocardiographic features and the need for histological confirmation through biopsy. We evaluated the prevalence of cardiac ATTR amyloidosis diagnosed noninvasively by the combination of the positive cardiac uptake on technetium (^{99m}Tc)-labeled pyrophosphate (PYP) scintigraphy and the absence of monoclonal protein among elderly heart failure patients. We also demonstrated the clinical features of cardiac ATTR amyloidosis.

Methods : We prospectively enrolled 38 consecutive patients, aged 70 years and older, who were treated for heart failure at our hospital between October 2017 and September 2018 and consented to undergo ^{99m}Tc-PYP scintigraphy. Experienced radiologists scored the cardiac uptake from grade 0 to 3, and grades 2 and 3 were defined as positive uptake. The clinical, echocardiographic, and electrocardiographic characteristics were recorded, and monoclonal protein studies were performed.

Results : Four patients showed positive cardiac uptake on the ^{99m}Tc-PYP scan, and two of them demonstrated grade 2 or 3 uptake and negative monoclonal protein. As one patient with grade 3 uptake and monoclonal protein was proven to have cardiac ATTR amyloidosis histologically, the proportion of cardiac ATTR amyloidosis was 7.9 % (3/38). We compared parameters including clinical, blood test and imaging characteristics between cardiac ATTR amyloidosis patients and others. The electrocardiographic voltage of the R-wave in the precordial leads was lower in cardiac ATTR amyloidosis.

Conclusions : This study indicated that cardiac ATTR amyloidosis should not be regarded as a rare cause of heart failure in elderly patients. *Shinshu Med J 69 : 37—44, 2021*

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Key words : transthyretin, amyloidosis, cardiomyopathy, ^{99m}Tc-PYP scintigraphy, heart failure

I Introduction

Cardiac amyloidosis is a progressive and life-threatening cardiomyopathy that is caused by extracellular deposition of amyloid fibrils in myocardial tissue. Amyloid deposition in the myocardium results in reduced ventricular compliance with impaired relaxation, while it may cause conduction abnormalities and arrhythmias in the conduction tissue. Cardiac transthyretin (ATTR) amyloidosis is one of the different forms of cardiac amyloidosis, which exists as a wild-type and hereditary subtype. It is caused by the protein transthyretin, which is prone to misfold and deposit as amyloid fibrils. The diagnosis of

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cardiac ATTR amyloidosis is frequently delayed or missed because there are no specific echocardiographic features, and histological confirmation through invasive biopsy has been traditionally required. It is estimated that the prevalence of undiagnosed cardiac ATTR amyloidosis is high among patients with heart failure, especially among the elderly. In fact, a previous population-based autopsy study revealed that wild-type ATTR amyloidosis can be found in 25 % of individuals over 85 years of age[1]. According to a more recent study, wild-type ATTR amyloidosis accounted for 13 % of the patients with HFpEF over 60 years based on ^{99m}Tc-labeled 3,3-disphosphono-1,2-propanodicarboxylic acid scintigraphy[2].

Radionuclide bone scintigraphy is remarkably sensitive and specific for cardiac ATTR amyloid and can detect cardiac ATTR amyloid deposits early in the course of the disease, sometimes before the appearance of echocardiographic abnormalities[3][4]. Immunoglobulin light chain (AL) amyloidosis also shows cardiac uptake during bone scintigraphy, but the uptake of radiotracer in cardiac ATTR amyloidosis is significantly higher than that in AL amyloidosis[5]. While a high uptake during bone scintigraphy is specific for cardiac ATTR amyloid, the presence of monoclonal protein is highly specific for AL amyloidosis. At the same time, a grade 2 or 3 cardiac uptake on the radionuclide scan in the absence of detectable monoclonal protein enables the diagnosis of cardiac ATTR amyloidosis with 100 % specificity[6]. For elderly patients, diagnosing amyloid cardiomyopathy without biopsy is particularly beneficial.

Until recently, there was no specific treatment for cardiac ATTR amyloidosis, but new generation drugs have proven effective in treating both hereditary and wild-type ATTR amyloidosis[7]. Tafamidis, which shows effectiveness against ATTR amyloidosis by binding to transthyretin and preventing tetramer dissociation and amyloidogenesis, has been approved for the treatment of ATTR amyloidosis in Japan since March 2019. This treatment option put importance into diagnosing cardiac ATTR amyloidosis.

We aimed to identify the frequency of cardiac ATTR amyloidosis among elderly patients with heart failure noninvasively using ^{99m}Tc-PYP scintigraphy. Second, we investigated the characteristics of patients with cardiac ATTR amyloidosis because the clinical features specific to cardiac ATTR amyloidosis were unrevealed.

Ⅱ Methods

A Patients

This was a single-center prospective study undertaken at Nagano Municipal Hospital. The subjects were consecutive patients hospitalized due to heart failure in our hospital between October 2017 and September 2018. The inclusion criteria were 1) aged 70 and over at admission, 2) complaining of symptoms matching the New York Heart Association (NYHA) classification Ⅱ-Ⅳ. The exclusion criteria were 1) complaining of NYHA Ⅱ-Ⅳ symptoms because of acute myocardial infarction, 2) unable to express symptoms because of comorbidity such as dementia, 3) judged impossible to undergo scintigraphy safely because of serious delirium. All patients provided written informed consent. The study protocol was approved by our institutional review board, and all procedures were in accordance with the Declaration of Helsinki.

B Data collection

1 Sociodemographic and other characteristics

Clinical characteristics were recorded by each attending physician during admission. Body mass index was calculated from height and weight at discharge. Congestive heart failure was defined on the basis of the history at admission or treatment with drugs. Hypertension and diabetes mellitus were defined on the basis of the clinical history or use of antihypertensive medication and oral hypoglycemic agents or insulin on admission.

2 Blood test

Blood parameters (estimated glomerular filtration rate, B-type natriuretic peptide, white blood count, and hemoglobin) were evaluated from the first blood test at admission.

3 Echocardiography

Echocardiography was performed by a physician

or skilled medical sonographer. The ejection fraction (EF) was measured by the modified Simpson method[8], and heart failure with preserved/reduced EF (HFpEF/HFrEF) was defined as EF ≥ 50 % and EF ≤ 40 %, respectively. Hypertrophy was defined as end-diastolic thickness of the interventricular septal or posterior wall ≥ 12 mm.

4 Electrocardiography

Electrocardiography (ECG) parameters were collected from the first ECG recorded during admission. Electrocardiographic left ventricular hypertrophy (LVH) was defined as a total amplitude of S1 and RV5/6 ≥ 3.5 mV according to the Sokolow-Lyon index[9]. Low voltage was diagnosed when the peak-to-peak QRS amplitude was less than 0.5 mV in all limb leads and/or less than 1 mV in all precordial leads.

C Diagnosis of ATTR

1 ^{99m}Tc-PYP scintigraphy

All patients underwent ^{99m}Tc-PYP scintigraphy, and cardiac retention was assessed on a planar image with a semi-quantitative visual score. Skilled radiologists non-blinded to the patients' data classified the uptake based on the following grading system from 0-3 : grade 0 = absent cardiac uptake ; grade 1 = mild uptake (less than bone) ; grade 2 = moderate uptake (equal to bone uptake) ; and grade 3 = high uptake (greater than bone uptake). Positive uptake included grades 2 and 3 cardiac uptake.

2 Monoclonal protein studies

Patients were also screened for monoclonal protein by immunofixation electrophoresis (IFE) of serum, IFE of urine, and by serum free light chain (sFLC) assay. The presence of monoclonal protein was defined as an abnormal sFLC ratio (<0.26 or >1.65) or the presence of a band on the IFE of serum or urine.

We evaluated the frequency of cardiac ATTR amyloidosis among our patients, diagnosed based on the finding of a grade 2 or 3 cardiac uptake on ^{99m}Tc-PYP scintigraphy in the absence of monoclonal protein.

D Statistical analyses

We compared the baseline characteristics including age, BMI, past history and blood test, echocardiographic, and ECG findings between cardiac ATTR amyloidosis patients and others to demonstrate the clinical features of cardiac ATTR amyloidosis. We used Fisher's exact test for categorical variables and Mann-Whitney U test or two-sample *t*-test for continuous variables to compare the two groups. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA), and a p-value < 0.05 was considered statistically significant.

Ⅲ Results

We enrolled 38 eligible consecutive patients. Baseline characteristics are shown in **Table 1**. The median age was 87 years, and females accounted for 61 % of all patients (23/38). The most frequent comorbidities were hypertension and atrial fibrillation, which both occurred in 61 % of patients. Based on the echocardiographic findings, half of the patients were considered to have HFpEF, and LVH was observed in 23 patients (47 % and 61 %, respectively).

All of the four patients with a positive uptake on the radionuclide scan demonstrated grade 3 uptake (**Table 2**). Monoclonal protein was detected in one patient, and in another patient with high cardiac uptake we missed the data for monoclonal protein. One patient with grade 3 uptake and monoclonal protein was histologically confirmed to have cardiac ATTR amyloidosis based on a biopsy sample obtained from the gastroduodenal mucosa. Accordingly, we diagnosed cardiac ATTR amyloidosis in three patients, and its frequency in our study population was 7.9 % (3/38).

Seven patients with missing monoclonal protein data were excluded in the comparison of characteristics between the three patients with cardiac ATTR amyloidosis and the other patients with heart failure (**Table 3**). Echocardiographic findings showed no differences, including LVH. Regarding the ECG findings, the voltage of V6 tended to be significantly lower among patients with cardiac ATTR amyloidosis than that among other patients (p = 0.007).

Ⅳ Discussion

In this study, 7.9 % of heart failure patients aged

Table 1 Summary of clinical, echocardiographic, and electrocardiographic characteristics of the 38 patients with heart failure included in the study

Age (years)	87	[82, 92]
Male gender, n (%)	15	(39%)
BMI (kg/m^2)	20	[18, 23]
Past history, n (%)		
Congestive heart failure	18	(47%)
Hypertension	23	(61%)
Diabetes Mellitus	9	(24%)
Atrial fibrillation	23	(61%)
Cerebral infarction	10	(26%)
Old myocardial infarction	2	(5%)
Echocardiographic findings		
LVEF (%)	46	[36, 61]
LVDd (mm)	44	[42, 53]
LVDs (mm)	35	[26, 39]
IVSd (mm)	12	[10, 13]
LVPWd (mm)	11	[10, 12]
HFpEF, n (%)	18	(47%)
HFrEF, n (%)	14	(37%)
LVH, n (%)	23	(61%)
≥moderate AS, n (%)	7	(18%)
≥moderate AR, n (%)	15	(39%)
≥moderate MS, n (%)	0	(0%)
≥moderate MR, n (%)	18	(47%)
Electrocardiographic findings		
SV1 (mV)	1.0	[0.6, 1.5]
RV5 (mV)	1.4	[1.0, 1.8]
RV6 (mV)	1.2	[0.8, 1.6]
SV1＋RV5/6 (mV)	2.4	[1.8, 3.4]
LVH, n (%)	9	(24%)
QRS duration (ms)	95	[80, 108]
Low voltage, n (%)	7	(18%)
CLBBB, n (%)	4	(11%)

Data are presented as the number with percentage (%) or the median with interquartile range [IQR].
BMI, body mass index ; LVEF, left ventricular ejection fraction ; LVDd, left ventricular end-diastolic diameter ; LVDs, left ventricular end-systolic diameter ; IVSd, interventricular septal diameter ; LVPWd, left ventricular posterior wall diameter ; HFpEF, heart failure with preserved ejection fraction ; HFrEF, heart failure with reduced ejection fraction ; LVH, left ventricular hypertrophy ; AS, aortic valve stenosis ; AR, aortic valve regurgitation ; MS, mitral valve stenosis ; MR, mitral valve regurgitation ; CLBBB, complete left bundle branch block ; IQR, interquartile range.

≥70 years were diagnosed with cardiac ATTR amyloidosis. This frequency indicates that cardiac ATTR amyloidosis should be considered as one of the causes of heart failure. Elderly patients with heart failure should be scanned with ^{99m}Tc-PYP scintigraphy to screen for cardiac ATTR amyloidosis.

Cardiac amyloidosis is considered a rare form of cardiomyopathy, but it is more likely that the diagnosis is delayed or missed because of its nonspecific echocardiographic features, absence of extracardiac symptoms, and need for histological confirmation, which can only be obtained through tissue biopsy. Gillmore et al.[6] demonstrated that an increased cardiac uptake during bone scintigraphy has more than 99 % sensitivity for cardiac ATTR amyloidosis, and the combined finding of high cardiac uptake on radionuclide scan with the absence of monoclonal protein was 100 % specific for cardiac ATTR amyloidosis.

An abnormal sFLC ratio is considered as a specific finding in AL amyloidosis, but it is also observed in monoclonal gammopathy of underdetermined significance (MGUS). The prevalence of MGUS in patients with wild-type cardiac ATTR amyloidosis was 39 %, as indicated by an abnormality in the sFLC ratio and/or serum IFE[10]. In our study, a patient who showed both grade 3 uptake on ^{99m}Tc-PYP scan and an abnormal sFLC ratio was considered to have cardiac ATTR amyloidosis not AL amyloidosis, which has a poor prognosis ; however, she survived until the age of approximately 80 years despite far progressed cardiac amyloidosis with a remarkable LVH in echocardiographic imaging. She underwent endoscopic biopsy from the gastroduodenal mucosa, and Congo red staining showed amyloid deposits and transthyretin detected by immunohistochemistry **(Fig. 1)**. We assumed that the abnormal sFLC ratio was caused by MGUS, but this could not be confirmed without a bone marrow aspiration.

This study has some limitations. First, each echocardiography was performed by a single physician or skilled medical sonographer, and accuracy and reproducibility of the parameters were unknown. Second, selection bias might have resulted from the fact that we did not use a standardized scale for evaluating the cognitive function of the enrolled patients, and the choice of patients was within the physician's discretion. We diagnosed cardiac ATTR amyloidosis patients following a previous study[6] ; however, true cardiac ATTR amyloidosis patients demonstrating the presence of monoclonal protein caused by monoclonal gammopathy of unknown significance and not by AL amyloidosis might be misdiagnosed.

Ⅴ Conclusion

This study indicated that cardiac ATTR amyloidosis should be considered one of the causes of heart failure in elderly heart failure patients. ^{99m}Tc-PYP scintigraphy is a useful tool to approach the etiology of heart failure noninvasively.

Ⅵ Acknowledgments

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Table 2 Patients (n = 4) with heart insufficiency and positive cardiac uptake on ^{99m}Tc-PYP scintigraphy

Gender	Age (years)	Monoclonal protein	^{99m}Tc-PYP uptake grade
Male	93	Data missing	3
Female	79	+	3
Male	79	−	3
Male	92	−	3

Table 3 Comparison of patients with cardiac transthyretin amyloidosis (n = 3) and remaining patients with heart insufficiency (n = 28)

	Cardiac ATTR amyloidosis (n = 3)		Other patients (n = 28)		P value
Age (years)	79	[79, 86]	88	[84, 92]	0.314
Male gender, n (%)	2	(67%)	10	(36%)	0.328
BMI (kg/m^2)	20	[20, 21]	21	[19, 24]	0.711
Past history, n (%)					
Congestive heart failure	2	(67%)	12	(43%)	0.425
Hypertension	2	(67%)	16	(57%)	0.624
Diabetes Mellitus	1	(33%)	8	(29%)	0.657
Atrial fibrillation	2	(67%)	18	(64%)	0.719
Cerebral infarction	0	(0%)	9	(32%)	0.343
Old myocardial infarction	0	(0%)	1	(4%)	0.903
Blood parameters at admission					
eGFR (mL/min/1.73m^2)	31	[27, 41]	46	[30, 57]	0.47
BNP (pg/mL)	760	[488, 814]	746	[472, 1417]	0.545
WBC (/μL)	4490	[3920, 5365]	6960	[5425, 8195]	0.045
Hb (g/dL)	11.1	[10.2, 12.3]	10.6	[9.2, 12.5]	0.798
Echocardiographic findings					
LVEF (%)	44	[31, 58]	46	[36, 60]	0.758
LVDd (mm)	40	[37, 44]	44	[43, 53]	0.195
LVDs (mm)	25	[25, 32]	35	[29, 39]	0.24
IVSd (mm)	15	[11, 17]	12	[10, 13]	0.67
LVPWd (mm)	10	[10, 15]	11	[10, 12]	0.803
HFpEF, n (%)	1	(33%)	13	(46%)	0.575
HFrEF, n (%)	1	(33%)	11	(39%)	0.672
LVH, n (%)	2	(67%)	17	(61%)	0.672
Electrocardiographic findings					
SV1 (mV)	1.3	[1.1, 1.5]	0.8	[0.5, 1.4]	0.321
RV5 (mV)	0.8	[0.8, 0.9]	1.4	[1.1, 1.7]	0.076
RV6 (mV)	0.5	[0.4, 0.6]	1.2	[1.0, 1.6]	0.007
SV1 + RV5/6 (mV)	1.9	[1.3, 2.2]	2.2	[1.8, 3.4]	0.21
LVH, n (%)	0	(0%)	6	(23%)	0.485
QRS duration (ms)	128	[114, 131]	94	[81, 101]	0.094
Low voltage, n (%)	1	(33%)	5	(18%)	0.488
CLBBB, n (%)	0	(0%)	3	(11%)	0.729

Data are presented as the number with percentage (%) or median with interquartile range [IQR].

BMI, body mass index ; eGFR, estimated glomerular filtration rate ; BNP, B-type natriuretic peptide ; WBC, white blood count ; Hb, hemoglobin ; LVEF, left ventricular ejection fraction ; LVDd, left ventricular end-diastolic diameter ; LVDs, left ventricular end-systolic diameter ; IVSd, interventricular septal diameter ; LVPWd, left ventricular posterior wall diameter ; HFpEF, heart failure with preserved ejection fraction ; HFrEF, heart failure with reduced ejection fraction ; LVH, left ventricular hypertrophy ; CLBBB, complete left bundle branch block ; IQR, interquartile range.

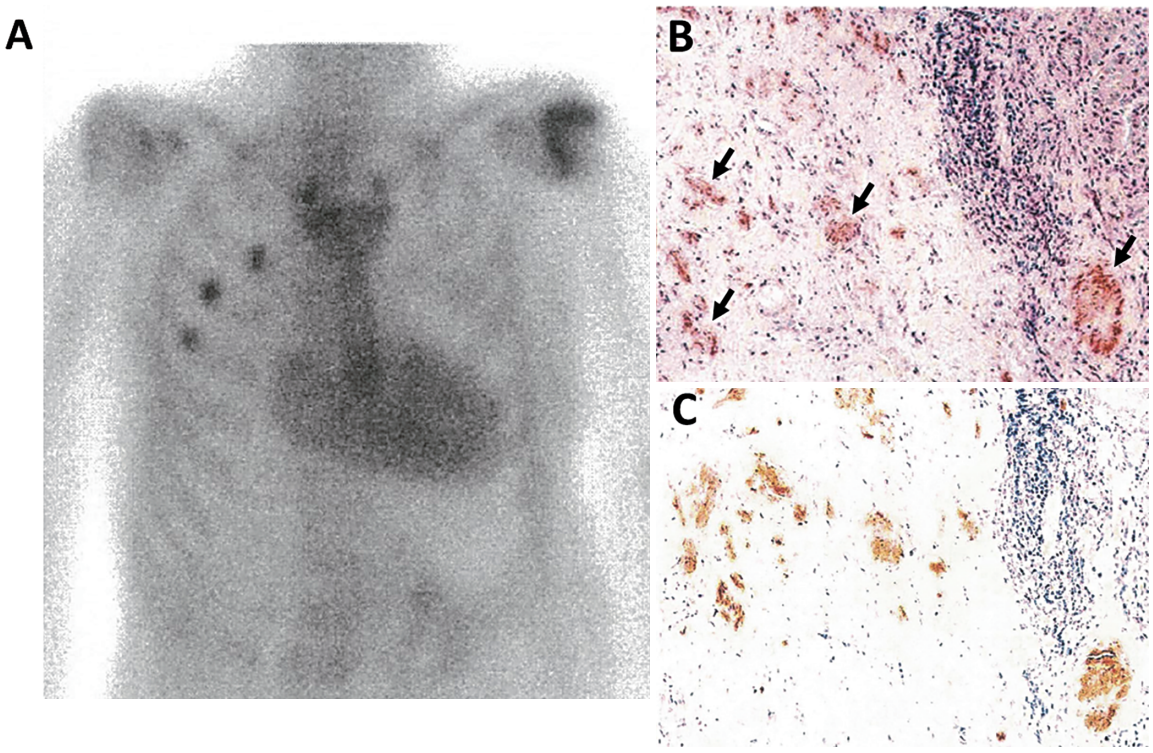

Fig. 1　Technetium-labeled pyrophosphate (99mTc-PYP) scintigraphy of the heart and histopathological correlation in a patient with cardiac ATTR amyloidosis

A：Technetium-labeled pyrophosphate (^{99m}Tc-PYP) scintigraphy scan shows grade 3 cardiac uptake.

B：Histology of the gastrointestinal mucosa biopsy from the same patient with congo red staining (× 200) showed positive deposit of amyloid (arrows).

C：Immunohistochemical staining detecting transthyretin (× 200) demonstrated the deposit of transthyretin amyloid in the same position with positive congo red staining.

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